# Formulation and Evaluation of Valproic Acid Suppositories for Children

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**Introduction:** Rectal suppositories of valproic acid were prepared using different lipophilic excipients: Suppocire NAI, Adeps solidus 50, Adeps solidus 3, Lipex 403, Cacao oleum. Each prepared suppository has been evaluated for various physical parameters like weight variation, disintegration and softening time and crushing (breaking) strength.
**Methods:** Suppositories were prepared by fusion method. The quantity of active drug (valproic acid) added to the suppositories was 200 mg, thus resulting 1.0 g suppositories. Prepared suppositories were visually inspected. Randomly selected suppositories were cut longitudinally and the surfaces were examined with naked eye. For determination of weight variation, 20 suppositories were weighed and the average weight was determined. Disintegration time, softening time and breaking strength of the prepared suppositories were determined according to the 5th European Pharmacopoeia.
**Results:** All the suppositories were free from pits, fissures and cracks. All formulas studied were disintegrated in less than 30 minutes. Valproic acid decreased the disintegration time of suppositories. The used excipient also influences the disintegration time, with a greater effect on the F1 formula (Suppocire NAI). After one month of preservation, the disintegration time of all formulas increased, but was less than 30 minutes. The softening time of the suppositories was the largest for the F1 formula (Suppocire NAI). The softening time decreases in the presence of valproic acid. The softening time and breaking strength increased for all formulas after one month.
**Conclusions:** The prepared suppositories were within the permissible range of physical parameters. The results obtained allow the selection of excipients in order to assure the optimum characteristics for prepared suppositories.

**Keywords:** valproic acid, suppositories, disintegration time, softening time, breaking strength

## Introduction

Valproic acid (2–propylpentanoic acid), by its official name 2-propylvaleric acid, was first synthesized in 1882 by Burton [1]. It is a chemical compound that has found clinical use as an anticonvulsivant in the treatment of epilepsy and bipolar disorder [2,3]. In epilepsy, valproic acid appears to act by increasing the concentration of gamma-aminobutyric acid (GABA) in the brain. A major advantage in pediatric therapy is rectal administration [3,4].

The objective of this study is to analyze several properties of prepared suppositories containing valproic acid (weight variation, disintegration time, softening time and breaking strength) [5,6,7].

## Materials and methods

### Materials

Valproic acid – Oakville, Canada; Adeps solidus 3 (Massa Estarinum 299) – Huls AG, Trisdorf Germany; Adeps solidus 50 (Witepsol W 35) – Huls AG, Trisdorf Germany; Suppocire NAI – Gattefosse, France; Cacao oleum – Nutraceuticals Group, Spain; Lipex 403 – Stéarinerie Dubois, France.

The drug and the excipients used in the preparation of the suppositories were of pharmaceutical grade.

### Formulation and preparation of suppositories

The rectal suppositories were obtained by melting and casting into shapes. The quantity of active drug (valproic acid) added to the suppositories was 200 mg, thus resulting 1.0 g suppositories (F6–F10). For comparison, suppositories without active drug (control) were prepared (F1–F5). The details of the formulations are presented in Table I.

The suppositories were kept at room temperature.

The physical parameter control of the suppositories was determined after 24 hours and one month of conservation.

### Evaluation of physical properties of suppositories

*Visual characterization*

The visual parameters such as fissuring, pitting and exudation were examined. The surface was examined with the naked eye for homogeneity.

*Weight variation*

Weight variation was determined according to the 10th Romanian Pharmacopoeia and 5th European Pharmacopoeia, using the KERN ABJ analytical balance. The Romanian pharmacopoeia establishes a 1–2 g weight for suppositories used in children. Individual weight may vary by ±10% compared to the calculated average weight [5,6,7]. Twenty suppositories were weighed and the average weight was determined. After that, the same suppositories were weighed individually. Mass variations in suppositories may appear if the suppository base was not correctly homogenized, if air was included into the base or if the mixture is too viscous at casting temperature [3].

*Disintegration time*

Disintegration time (Dt) was determined according to the 5th European Pharmacopoeia using QC-21 Disintegration Test System, Hanson Research, Chatsworth, CA, USA. Six suppositories of each tested formula were placed in a special glass container with perforated ends and immersed in a water bath maintained at 37±1ºC.

Disintegration is considered to be achieved when the moulded suppository is completely dissolved or has separated into its component parts. Disintegration occurs in no more than 30 minutes for lipofilic suppositories [7].

*Softening time*

The softening test measures the liquefaction time of rectal suppositories. Suppository softening time defines the time in which a suppository immersed in water becomes soft enough not to exert a resistance against a well defined load.

We used an Erweka PM 30 apparatus (Germany), we placed the glass tube containing 10 ml of water in a water-bath and set it to 36.5±0.5ºC. We fixed the glass tube vertically and immersed to a depth of at least 7 cm below the surface, without touching the bottom of the water-bath. We introduced a suppository into the tube followed by the rod with the free gliding plastic cover into the glass tube until the metal needle touched the flat end of the suppository. We put the cover on the tube (beginning of time measurement). We noted the time elapsed until the rod sunk down to the bottom of the glass tube and the mark ring reached the upper level of the plastic cover [7]. The results represent the average of 3 determinations.

**Table I. Composition of valproic acid suppositories**

| Components | Composition (g) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 |
| Valproic acid | – | – | – | – | – | 0.20 | 0.20 | 0.20 | 0.20 | 0.20 |
| Suppocire NAI | 1.00 | | – | – | – | 0.80 | – | – | – | – |
| Witepsol W 35 | – | 1.00 | | – | – | – | 0.80 | – | – | – |
| Massa Estarinum 299 | – | | 1.00 | | – | – | – | 0.80 | – | – |
| Lipex 403 | – | | – | 1.00 | | – | – | – | 0.80 | – |
| Cacao oleum | – | | – | – | 1.00 | – | – | – | – | 0.80 |

*Breaking strength*

Breaking strength was determined measuring the mass (in kilograms) that a suppository can handle without breaking, using Erweka suppositories hardness tester GMB H, Germany. We checked that the apparatus is vertical and heated the thermostated chamber to 25ºC. We placed the suppository vertically between the jaws of the sample holder with the point upwards. The test chamber was closed and we waited for 1 minute before adding the first 200 g disc. We waited again for 1 minute and added another disc, repeating the operation until the suppository collapsed at the breaking point. The initial mass applied was 600 g [6,7]. The results represent the average of 10 determinations.

## Results

### Visual characterization

We obtained torpedo shaped suppositories, with a homogenous aspect, without air bubbles, free from pits, fissures

**Table II. Weight variation for F1–F5 control formulations**

| Sample | F1 | | F2 | | F3 | | F4 | | F5 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | m (g) | D (%) | m (g) | D (%) | m (g) | D (%) | m (g) | D (%) | m (g) | D (%) |
| 1 | 1.0143 | +0.0197 | 1.0124 | -0.3151 | 1.0186 | +0.3547 | 1.0123 | -0.3543 | 1.0125 | -0.2954 |
| 2 | 1.0141 | 0 | 1.0168 | +0.1182 | 1.0116 | -0.3350 | 1.0108 | -0.5020 | 1.0168 | +0.1280 |
| 3 | 1.0125 | -0.1578 | 1.0104 | -0.5120 | 1.0164 | +0.1379 | 1.0132 | -0.2658 | 1.0153 | -0.0197 |
| 4 | 1.0121 | -0.1972 | 1.0192 | +0.3545 | 1.0170 | +0.1970 | 1.0138 | -0.2067 | 1.0133 | -0.2166 |
| 5 | 1.0127 | -0.1380 | 1.0167 | +0.1083 | 1.0113 | -0.3645 | 1.0128 | -0.3051 | 1.0145 | -0.0985 |
| 6 | 1.0143 | +0.0197 | 1.181 | +0.2462 | 1.0126 | -0.2364 | 1.0129 | -0.2953 | 1.0125 | -0.2954 |
| 7 | 1.0136 | -0.0493 | 1.0173 | +0.1674 | 1.0195 | +0.4433 | 1.0156 | -0.0295 | 1.0193 | +0.3742 |
| 8 | 1.0191 | +0.4930 | 1.0085 | -0.6991 | 1.0155 | +0.0492 | 1.0127 | -0.3150 | 1.0110 | -0.4431 |
| 9 | 1.0157 | +0.1578 | 1.0128 | -0.2757 | 1.0101 | -0.4827 | 1.0169 | +0.0984 | 1.0195 | +0.3939 |
| 10 | 1.0134 | -0.0690 | 1.0122 | -0.3348 | 1.0127 | -0.2266 | 1.0172 | +0.1280 | 1.0150 | -0.0492 |
| 11 | 1.0184 | +0.4240 | 1.0185 | +0.2855 | 1.0157 | +0.0690 | 1.0198 | +0.3839 | 1.0141 | -0.1379 |
| 12 | 1.0154 | +0.1282 | 1.0125 | -0.3052 | 1.0149 | -0.0099 | 1.0182 | +0.2264 | 1.0182 | +0.2659 |
| 13 | 1.0184 | +0.4240 | 1.0111 | -0.4431 | 1.0113 | -0.3645 | 1.0155 | -0.0394 | 1.0195 | +0.3939 |
| 14 | 1.0124 | -0.1676 | 1.0154 | -0.0197 | 1.0115 | -0.3448 | 1.0178 | +0.1870 | 1.0141 | -0.1379 |
| 15 | 1.0126 | -0.1479 | 1.0184 | +0.2757 | 1.0124 | -0.2562 | 1.0182 | +0.2264 | 1.0166 | +0.1083 |
| 16 | 1.0122 | -0.1874 | 1.0182 | +0.2560 | 1.0199 | +0.4828 | 1.0174 | +0.1477 | 1.0176 | +0.2068 |
| 17 | 1.0131 | -0.0986 | 1.0185 | +0.2855 | 1.0114 | -0.3547 | 1.0199 | +0.3937 | 1.0159 | +0.0394 |
| 18 | 1.0132 | -0.0887 | 1.0178 | +0.2166 | 1.0194 | +0.4335 | 1.0156 | -0.0295 | 1.0133 | -0.2166 |
| 19 | 1.0122 | -0.1873 | 1.0184 | +0.2757 | 1.0197 | +0.4631 | 1.0197 | +0.3741 | 1.0167 | +0.1182 |
| 20 | 1.0127 | -0.1380 | 1.0187 | +0.3052 | 1.0194 | +0.4335 | 1.0181 | +0.2166 | 1.0146 | -0.0886 |
| Average mass (M) | 1.0141 | – | 1.0153 | – | 1.0150 | – | 1.0159 | – | 1.0155 | – |
| $M_{max}$ | 1.0191 | – | 1.0192 | – | 1.0199 | – | 1.0199 | – | 1.0195 | – |
| $M_{min}$ | 1.0121 | – | 1.0085 | – | 1.0101 | – | 1.0108 | – | 1.0110 | – |
| $M_{max}$–M | 0.005 | – | 0.0039 | – | 0.0049 | – | 0.004 | – | 0.004 | – |
| M–$M_{min}$ | 0.002 | – | 0.0068 | – | 0.0049 | – | 0.0051 | – | 0.0045 | – |

**Table III.** Weight variation for F6–F10 formulations

| Sample | F6 | | F7 | | F8 | | F9 | | F10 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | m (g) | D (%) | m (g) | D (%) | m (g) | D (%) | m (g) | D (%) | m (g) | D (%) |
| 1 | 1.0155 | +0.5147 | 1.0163 | -0.0098 | 1.0015 | -0.9403 | 1.0014 | -1.2036 | 1.0112 | -0.1087 |
| 2 | 1.0134 | +0.3068 | 1.0194 | +0.2952 | 1.021 | +1.0591 | 1.0126 | -0.0987 | 1.0183 | +0.5927 |
| 3 | 1.0109 | +0.0594 | 1.0187 | +0.2263 | 1.0112 | +0.0891 | 1.0125 | -0.1085 | 1.0095 | -0.2766 |
| 4 | 1.0114 | +0.1089 | 1.0171 | +0.0688 | 1.0122 | +0.1881 | 1.0111 | -0.2467 | 1.0017 | -1.0471 |
| 5 | 1.013 | +0.2672 | 1.0129 | -0.3443 | 1.0024 | -0.7819 | 1.0098 | -0.3749 | 1.0176 | +0.5236 |
| 6 | 1.008 | -0.2277 | 1.0173 | +0.0886 | 1.0008 | -0.8710 | 1.0156 | +0.1973 | 1.0006 | -1.1558 |
| 7 | 1.0002 | -0.9997 | 1.0138 | -0.2558 | 1.0034 | -0.6829 | 1.0171 | +0.3453 | 1.0125 | +0.0198 |
| 8 | 1.014 | +0.3662 | 1.0186 | +0.2165 | 1.0057 | -0.4553 | 1.0165 | +0.2861 | 1.0169 | +0.4544 |
| 9 | 1.0129 | +0.2573 | 1.0133 | -0.3050 | 1.0158 | +0.5444 | 1.0182 | +0.4538 | 1.0184 | +0.6026 |
| 10 | 1.0145 | +0.4157 | 1.0138 | -0.2558 | 1.0116 | +0.1287 | 1.0177 | +0.4045 | 1.0097 | -0.2568 |
| 11 | 1.0135 | +0.3167 | 1.0136 | -0.2755 | 1.0146 | +0.4256 | 1.0077 | -0.5821 | 1.0073 | -0.4939 |
| 12 | 1.0176 | +0.7226 | 1.0161 | -0.0295 | 1.0121 | +0.1782 | 1.0143 | +0.0691 | 1.0093 | -0.2964 |
| 13 | 1.0041 | -0.6137 | 1.0157 | -0.0689 | 1.0176 | +0.7226 | 1.0192 | +0.5525 | 1.0191 | +0.6717 |
| 14 | 1.0117 | +0.1386 | 1.0194 | +0.2952 | 1.0038 | -0.6434 | 1.0119 | -0.1677 | 1.0088 | -0.3458 |
| 15 | 1.0082 | -0.2078 | 1.0178 | +0.1377 | 1.0187 | +0.8314 | 1.019 | +0.5326 | 1.0171 | +0.4741 |
| 16 | 1.0004 | -0.9799 | 1.0179 | +0.1476 | 1.0178 | +0.7424 | 1.0151 | +0.1480 | 1.0113 | -0.0988 |
| 17 | 1.0096 | -0.0692 | 1.0164 | 0 | 1.0151 | +0.4751 | 1.0161 | +0.2466 | 1.0178 | +0.5433 |
| 18 | 1.0035 | -0.6730 | 1.0134 | -0.2952 | 1.0013 | -0.8908 | 1.0167 | +0.3058 | 1.0138 | +0.1481 |
| 19 | 1.0185 | +0.8116 | 1.0167 | +0.0295 | 1.0163 | +0.5939 | 1.0125 | -0.1085 | 1.0127 | +0.0395 |
| 20 | 1.0042 | -0.6038 | 1.0196 | +0.3148 | 1.0039 | -0.6335 | 1.0073 | -0.6216 | 1.0126 | +0.0296 |
| Average mass (M) | 1.0103 | – | 1.0164 | – | 1.0103 | – | 1.0136 | – | 1.0123 | – |
| $M_{max}$ | 1.0185 | – | 1.0196 | – | 1.021 | – | 1.0192 | – | 1.0191 | – |
| $M_{min}$ | 1.0002 | – | 1.0129 | – | 1.0008 | – | 1.0014 | – | 1.0006 | – |
| $M_{max}$–M | 0.0082 | – | 0.0032 | – | 0.0107 | – | 0.0056 | – | 0.0068 | – |
| M–$M_{min}$ | 0.0101 | – | 0.0035 | – | 0.0095 | – | 0.0122 | – | 0.0117 | – |

**Table IV.** Disintegration time ($D_t$) of the suppositories

| Formula | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 |
|---|---|---|---|---|---|---|---|---|---|---|
| $D_t$ ± SD (min) after 24 h | 15.07±0.76 | 14.09±0.58 | 11.57±0.68 | 12.52±0.82 | 8.07±0.43 | 7.36±0.79 | 7.05±0.38 | 7.09±0.43 | 7.42±0.63 | – |
| $D_t$ ± SD (min) after 1 month | 15.15±0.90 | 14.51±0.67 | 12.12±0.84 | 13.36±0.97 | 8.52±0.89 | 7.71±0.64 | 7.47±0.52 | 7.56±0.35 | 8.09±0.48 | – |

**Table V.** Softening time of the suppositories

| Formula | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 |
|---|---|---|---|---|---|---|---|---|---|---|
| Softening time ± SD (min) after 24 h | 7.55±0.45 | 7.01±0.35 | 4.38±0.41 | 5.45±0.45 | 2.5±0.15 | 1.24±0.1 | 1.15±0.1 | 1.16±0.1 | 1.38±0.1 | – |
| Softening time ± SD (min) after 1 month | 8.21±0.65 | 7.47±0.54 | 5.52±0.43 | 6.06±0.38 | 3.04±0.24 | 1.51±0.16 | 1.44±0.13 | 1.55±0.15 | 1.65±0.17 | – |

and cracks. The suppositories were homogenous on the surface and also on the inside. These characteristics did not change after a 30 day period of conservation.

### Weight variation

The individual weight of the prepared formulas, the average mass and percentage of deviation are presented in Tables II and III.

Weight variations were in conformity with the $5^{th}$ European Pharmacopoeia for each formula. The percentage of deviation was less than 5%.

### Disintegration time

According to Table IV, our prepared suppositories were in conformity with the rules stated by the pharmacopoeias, with the exception of those manufactured with Cacao oleum (cocoa butter), which melted in the box (package).

The used excipient influences the disintegration time ($D_t$), this parameter being more increased in the case of F1 formula with Suppocire NAI (15.07 minutes).

All the studied formulas were disintegrated in less than 30 minutes. Valproic acid reduces the disintegration time of suppositories: F6 – 7.36 minutes.

**Table VI.** Breaking strength of studied suppositories

| Formula | Breaking strength (kg) ± SD | | Formula | Breaking strength (kg) ± SD | |
|---|---|---|---|---|---|
| | 24 h | 1 month | | 24 h | 1 month |
| F1 | 1.00±0.024 | 1.25±0.031 | F6 | 0.70±0.012 | 0.80±0.022 |
| F2 | 0.90±0.019 | 1.20±0.028 | F7 | 0.60±0.015 | 0.70±0.026 |
| F3 | 0.80±0.017 | 1.10±0.015 | F8 | <0.60 | <0.60 |
| F4 | 0.90±0.011 | 1.20±0.030 | F9 | <0.60 | 0.70±0.018 |
| F5 | 0.70±0.034 | 0.80±0.018 | F10 | – | – |

### Softening time

The softening time of the suppositories determined after 24 h and 1 month from preparation is shown in Table V.

The softening time of the suppositories was the largest for the F1 formula (Suppocire NAI): 7.55 minutes. The presence of valproic acid reduced the softening time of suppositories: F6 – 1.24 minutes. The softening time increased for all formulas after one month.

### Breaking strength

Ten suppositories of each formula were tested. The results are presented in Table VI.

For all formulas preparated with valproic acid, breaking strength decreased in line with disintegration and softening time: F1 – 1.01±0.031 kg, F6 – 0.73±0.067 kg. The hardness of each formula increased after one month: F1 – 1.23±0.048 kg, F6 – 0.82±0.042 kg.

## Discussions

Valproic acid reduces suppositories' disintegration time because it is a liquid substance. After a month of preservation, the disintegration time of all formulas increased, but was still less than 30 minutes. In F10 formula we couldn't assess disintegration time because valproic acid caused a considerable lowering of the melting point of cacao oleum when warmed with it (they were melted in the box). In terms of softening time, the prepared suppositories were in conformity with the rules stated by the pharmacopoeias, with the exception of those prepared with Cacao oleum (cocoa butter), which melted in the box (package). Cocoa butter is an admixture of C16–C18 saturated and non-saturated fatty acids and has a very marked polymorphism due to its composition. Four allotrope forms are known: $\alpha$, $\beta'$ and $\gamma$, which are unstable, and a stable $\beta$ form. Its stable form recommends it for use in suppository manufacturing, but it cannot be used for incorporating substances that lower its melting point. The hardness of valproic acid suppositories decreases linearly with disintegration and softening time.

## Conclusions

The used excipient and properties of the drug influence the disintegration time, this parameter being more increased in the case of F1 formula (Suppocire NAI). The softening time and the disintegration time decrease in the presence of valproic acid and after one month the softening and disintegration time increase for all formulas. The hardness of valproic acid suppositories decreases in line with disintegration and softening times.

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